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Tenofovir–best hope for treatment of chronic hepatitis B infection?

LIVER

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Original Article

ABSTRACT

Background/Aims: To evaluate the effectiveness of tenofovir in patients with chronic hepatitis B infection in a real life setting.

Materials and Methods: We performed a retrospective analysis of data from 164 patients with chronic hepatitis B who were treated with Tenofovir. Eighty-six patients (52.4%) were naïve. Seventy-seven (46.9%) patients were previously treated with anti-viral drugs, including standard interferon (n=4), pegylated (PEG) interferon (n=14), standard interferon together with lamivudine (n=13), lamivudine alone (n=41), adefovir (n=2), lamivudine together with adefovir (n=1), and entecavir (n=2). Six patients (3.7%) had liver cirrhosis before treatment of tenofovir.

Results: The patients who have hepatitis B viral DNA>104 copy/mL with chronic hepatitis B infection were included in the treatment of Tenofovir. Average follow up time was 30.31±14.33 months. HBV DNA negativity and alanine aminotransferase (ALT) normalization were 86.5% and 71.3%, respectively, at the last visit. Hepatitis B e-Antigen (HBeAg) seroconversion occurred in 11 (19.6%) out of 164 patients. During the follow-up period, 4 (2.4%) patients developed liver cirrhosis and in 5 (3%) patients hepatocellular carcinoma (HCC) occurred out of 164 patients. HBsAg seroconversion occurred in one patient (0.6%).

Conclusion: Tenofovir can be used safely and successfully in those patients that were naive, experienced with immune modulators and/or antivirals, HBeAg-positive, and HBeAg-negative patients.

Keywords: HBV, Tenofovir treatment, sustained virological response, HBeAg seroconversion

INTRODUCTION

Hepatitis B virus (HBV) is a global-health threat that infects more than 350 million people worldwide. HBV is the cause of chronic liver disease in 5% of adults and 80% of children who acquire the infection. Twenty–forty percent of patients with chronic hepatitis B may progress to liver cirrhosis. Patients with liver cirrhosis due to HBV infection may experience decompensation at a rate of 2%–5% annually (1). The risk of developing hepatocellular carcinoma (HCC) within 5 years is 17% in eastern and 10% in western countries. More than 600.000 people worldwide die from liver cirrhosis or complications of cirrhosis every year. The 5 year survival rate for patients with decompensated liver cirrhosis due to HBV is 17%–35% (2,3).

The treatment of HBV infection aims to suppress HBV DNA replication, decrease necroinflammation, prevent progressive fibrosis, HCC, and finally to eradicate HBV (4-6). Until now, it has been difficult to eliminate HBV because of its integration in the host genome as covalently close circular DNA (cccDNA). The latter serves

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as the transcriptional template for host RNA polymerase II, an enzyme that produces a series of sub-genomic transcripts (3).

Presently, there are six drugs relied upon the treatment of HBV infection. According to their sequence of approval, conventional and pegylated interferons (immune modulators), and five nucleos(t)ide analogs: lamivudine, adefovir, entecavir, telbivudine, and tenofovir (4-6), are in use. There are several factors which influence the sustained virological response (SVR), such as viral load, HBeAg positivity, level of HBsAg, ALT levels, gender, race, body mass index, history of acute viral hepatitis, and co-infections (7).

The aim of this study is to evaluate the effectiveness of tenofovir, in terms of HBV DNA suppression, HBeAg and HBsAg seroconversion, and ALT normalization in patients with chronic hepatitis B infection in actual life settings.

MATERIALS AND METHODS

One hundred and sixty-four patients who were diagnosed with chronic hepatitis B infection were approved for this coordinated study. The study was conducted retrospectively. Patients with co-infection and systemic disorders were excluded. The subjects included fifty-three (32.3%) females and one hundred eleven (67.7%) males, whose average age was 45.34±14.19 years (the youngest being 19 years and the oldest being 83 years). Eighty-six patients (52.4%) were naive and treated with tenofovir. Seventy-seven (46.9%) patients were previously treated with anti-viral drugs with standard interferon (n=4), PEG interferon (n=14), standard interferon together with lamivudine (n=13), lamivudine alone (n=41), adefovir (n=2), lamivudine together with adefovir (n=1), and entecavir (n=2). Six patients (3.7%) had liver cirrhosis before treatment with tenofovir. All patients had HBV DNA levels in the upper 10^4 copies/mL, average was $5.5x10^8$ copies/mL. The average ALT level was 103.52±126. 67 IU. Fifty-six patients (34.3%) were HBeAg-positive (Table 1). All patients were monitored from 6 to 62 months with an average follow-up time of 30.31±14.33 months. Patients were checked every 6 months in terms of suppression of HBV DNA, HBeAg negativization and HBeAg seroconversion, HBsAg negativizasion and HBsAg seroconversion, ALT normalization, and occurrence of liver cirrhosis and hepatocellular cancer (Table 1).

Table 1. Patient baseline demographics, clinical and laboratory characteristics

Age	45.34±14.19
Follow-up time	Average 30.31±14.33 months (Minimum 6, maximum 62)
Gender (female/male)	53 (32.3%)/111(67.7%)
Naïve patients	86 (52.4%)
Immune modulators and/or antiviral treatment experienced patients: Drugs	Number of patients
Standard interferon	4
PEG interferon	14
Lamivudine	41
Interferon+Lamivudine	13
Adefovir	2
Lamivudine+Adefovir	1
Entecavir	2
Liver cirrhosis after Tenofovir treatment	4 (2.4%)
Liver cirrhosis before Tenofovir treatment	6 (3.7%)
Occurrence of hepatocellular carcinoma	5 (3%)
Baseline ALT levels	103.52+126.67 IU/mL
Baseline HBV DNA levels	$5.5x10^8$ copy/mL
The first visit HBeAg positivity	56 (34.3%)
HBeAg seroconversion rate	11 (19.6%)
HBsAg seroconversion rate	1 (0.6%)

*PEG: pegylated; *ALT: alanine aminotransferase; *HBV: hepatitis B virus

Data was expressed as mean±standard deviation. Independent *t*-test or paired samples *t*-test was used for group comparisons where available. Categorical variables were compared with Chi^2 test. Logistic regression analysis was used to identify independent factors related with SVR. Statistical significance was set at a p-value of less than 0.05. All statistical analysis was made using Statistical Package for the Social Sciences 16.0 (SPSS software, SPSS Inc, Chicago, Illinois, USA).

RESULTS

From a period of 6 to 24 months, HBV DNA suppression gradually increased from 70.6%–89% with treatment of tenofovir. At the 24th month of treatment, 88.9 % suppression was reached and continued to plateau up to the 36th month and longer (Table 2).

During the final visit, HBV DNA was negative in 141 (86.5%) of the patients (Figure1).

However, HBV DNA was positive in 13 (7.9%) patients. The follow-up time for those patients was 26.33±14.47 (minimum, 12; maximum, 48) months. Hepatic flares were seen in nine (5%) out of 13 patients. HBV DNA levels were not checked for ten

Table 2. HBV DNA negativity and ALT normalization from 6 months to final visit

	Negativity of HBV DNA	Normalization of ALT
6 months (negative/positive)	70.6% (84/35)	70.2% (99/42)
12 months (negative/positive)	78.9% (116/31)	68% (104/49)
24 months (negative/positive)	88.9% (96/12)	73.75% (84/30)
36 months (negative/positive)	89% (65/8)	71.6% (53/21)
Final visit (negative/positive/flare) (Average follow up time: 30.31±14.33) months	86.5% (141/13/9)	71.3% (117/31/16)

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Table 3. Impact of clinical and laboratory parameters on HBV DNA negativity

	Patients with HBV DNA become negative after treatment	Patients with HBV DNA positive after treatment	p value
Gender (Female/Male)	46/95	7/15	0.940
Age (Years)	45.82±13.91	41.09±14.95	0.143
Follow up time	30.54±14.41	29.68±13.91	0.793
HBeAg-negative	93.4%	6.6%	0.001
HBeAg-positive	75.0%	25.0%	
Naive patients			
Yes	83.3%	16.7%	0.257
No	89.4%	10.6%	
Patients with higher (>10^5 copy/mL) viral load	83.3%	16.7%	0.189
Patients with low (<10^5 copy/mL) viral load	90.6%	9.4%	
HBV DNA Log10, before treatment	6.06±2.21	7.03±2.33	0.067

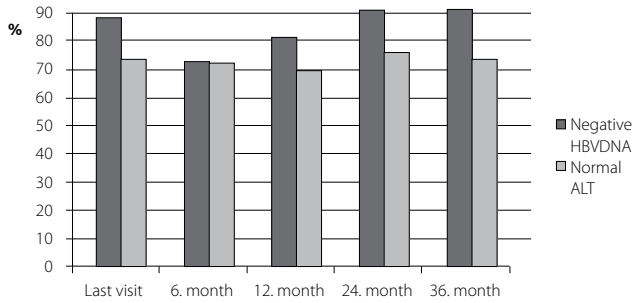

Figure 1. Changes of HBV DNA and ALT levels during tenofovir treatment period.

patients during the final visit. There were no statistical differences between patients with HBV DNA>10^5 copy/mL and <10^5 copy/mL in terms of HBV DNA negativity after the treatment with tenofovir (p=0.189) (Table 3).

ALT levels at baseline were 103.52±126.67 IU. After 6 months of treatment with tenofovir, ALT levels were reduced to normal in 70.2% of patients and remained so until the last visit in 71.3% of the patients (Table 2).

There was no statistical difference between the two groups, naive and treatment experienced with immune modulators and/or antivirals, in terms of SVR and ALT normalization after the treatment with tenofovir (p=0.257, Table 3).

HBeAg was positive in 56 (34.3%) out of 164 patients. HBV DNA was negative in 75.0% of 56 patients with HBeAg-positive, while HBV DNA was negative in 93.4% of patients with HBeAg negative. However, in 25% of 56 patients, HBV DNA was still positive at the last visit, while HBV DNA was positive in 6. 6% of patients with HBeAg negative (p=0.001). HBeAg seroconversion occurred in 11 (19.6%) patients. In the final follow-up visit, HBeAg status was not checked in eleven patients. There was no statistical difference in terms of SVR in the patients with or without HBeAg seroconversion at 6 months, although normalization of ALT levels and the negativity rate of HBV DNA were higher in patients with seroconversion of HBeAg than in patients without HBeAg seroconversion. Regression analysis showed that there were no predictive factors between age, gender, follow up time, baseline HBV DNA, and ALT levels in terms of negativity of HBeAg (Table 4; p=0.090, p=0.500, p=0.409, p=0.457, and p=0.436, respectively).

Regression analysis was used in order to predict SVR among parameters of gender, age, follow-up time, HBV DNA levels, ALT levels, and HBeAg positivity (p values were p=0.940, p=0.143, p=0.793, p=0.067, p=0.257, p=0.189, respectively). However, HBeAg negativity was the only predictive factor used to obtain SVR (p=0.001). During the follow-up period, 4 (2.4%) patients developed liver cirrhosis and HCC occurred in five (3%) patients out of 164.

DISCUSSION

Immune modulators were effective in decreasing liver cirrhosis and HCC, while increasing the survival rate in 20%–30% of patients with both HBeAg-positive and HBeAg-negative chronic HBV infection, particularly in young female patients with low viral load (<10^8 copy/mL, genotype A or B, HBeAg-positive) (8). Recent data proved that if HBV-DNA decreases more than 2 log 10 and HBsAg decreases more than one log 10 at 12 weeks of treatment, SVR may increase nearly 39% (8-12). An absence of HBsAg declines together with a <2 log reduction of HBV DNA at week 12 of PEG interferon treatment, which is an important indication for stopping the treatment (13).

Immune modulator drugs act by restoring the host immune control of viral replication. The most important advantages of PEG interferon treatment are long lasting remission, finite duration, and absence of resistance. However, weekly subcutane-

Table 4. The impact of clinical and laboratory characteristics on HBeAg seroconversion

	Patients without HBeAg seroconversion n:34	Patients with HBeAg seroconversion n:11	p
Gender (Female/Male)	13/21	2/9	0.220
Age	36.79±11.73	46.27±19.06	0.054
Average follow up time	35.67±13.59	27.09±14.40	0.080
Baseline HBV DNA (log 10)	7.06±2.25	7.34±1.46	0.712
Baseline ALT levels	92.20±98.67	177.09±260. 93	0.116
HBVDNA negative at 6th months	33.3% (8/24)	80% (4/5)	0.054
ALT normal at 6th month	55.6% (15/27)	88.9% (8/9)	0.071

ous injections are less effective in patients with a higher viral load (>10^9 copy/mL), genotype D and C, experiencing the usual common adverse side effects, are the main disadvantages of these drugs (9).

Interferon based immunomodulatory therapies have been replaced by nucleos(t)ide analogues, which have better antiviral effects and safety profiles for the treatment of HBV infection (7).

Treatment with nucleos(t)ide analogs in chronic hepatitis B infection rapidly suppresses viral load, decreases occurrence of liver cirrhosis, increases seroconversion of HBeAg with minimal side effects, and length of survival (14-18). The main disadvantages of treatment with nucleos(t)ide analogs are the risks of developing resistance to prolonged therapy, indefinite duration of treatment, and less increases in HBeAg and HBsAg seroconversion, particularly in patients who are HBeAg-negative (19,20).

Tenofovir disoproxil fumarate (TDF) is an oral prodrug of tenofovir that inhibits the activity of viral HBV DNA polymerase, while terminating viral DNA chain elongation and stopping viral genome replication, having a high genetic barrier to resistance. It is eliminated without changing the glomerular filtration and tubular secretion (21).

In two double-blind randomized studies (Study 102 and 103), daily doses of 300 mg of tenofovir were proven to be more effective than daily treatments of 10 mg adefovir in reducing viral suppression in 93% and 76% of patients, both HBeAg-negative and HBeAg-positive, respectively; a reduction of HBsAg was noted in 3% of patients treated with Tenofovir at 48 weeks (22). One hundred twenty-nine patients with high viral load (>9 log 10 IU/mL) were randomly treated with adefovir (10 mg/day, n=47) or tenofovir (300 mg/day, n=82) for a treatment period of 48 weeks. Tenofovir treatments had undetectable DNA levels at a rate of 99.2% and 98.3% in low viral load and high viral load groups, respectively, at week 240. Patients with high viral loads took longer time to achieve undetectable HBV DNA than that by patients with low viral load groups. The histopathological regression rate was similar in both the adefovir and tenofovir treated groups (23). In an extension of these studies, patients at 288 weeks showed that tenofovir monotherapy maintains effective viral suppression with no evidence of tenofovir resistance (24).

Regression of liver cirrhosis and fibrosis was reported at the rate of 87% and 51%, respectively, with tenofovir treatment in 348 patients with chronic HBV infection and liver biopsy base line, at week 240 (25). Tenofovir was shown to be both effective and safe in decompensated chronic HBV liver disease (26).

In a prospective double-blind study in patients with lamivudine resistance, using tenofovir alone (300 mg, n=141) or in combination with emtricitabine (FTC 200 mg, n=139), had undetectable HBV DNA levels in 89.4% and 86.3% of patients, respectively, at the 96th week. There was no statistical importance between the two groups in terms of HBV DNA negativity (27).

The patients with suboptimal virological response to adefovir treatment (10 mg/day) at the 96th week were randomized to tenofovir alone (300 mg/day, n=53) or in combination with tenofovir and emtricitabine (FTC: 200 mg/day, n=52) in terms of efficacy and safety of tenofovir in the 168th week. Long term viral suppression was maintained at the 168th week in 82% of patients who received tenofovir monotherapy and in 84% of patients treated with a combination of emtricitabine. There was no resistance against tenofovir alone or in combination with emtricitabine throughout the 168 week period. Both treatments were well tolerated (28).

Similarly, 13 out of 29 chronic HBV patients with suboptimal response or multidrug resistance were treated with tenofovir (300 mg/day) as a rescue therapy. Undetectable rates of HBV DNA levels were 86.2% and 96.6% at 12 and 24 months, respectively. The presence of specific mutations or combination therapy with lamivudine or entecavir did not influence the SVR rate. There were no adverse events with tenofovir treatment (29).

Fourteen (2.9%) patients with suboptimal response (failure to achieve >1 log 10 HBV DNA reduction in 24 weeks of treatment with entecavir (0.5 mg/day) were among the 482 entecavir treated patients switched to tenofovir (300 mg/day)

monotherapy. All 14 patients achieved undetectable HBV-DNA and ALT normalization. Tenofovir treatment was safe and well tolerated (30).

Entecavir monotherapy (0.5 mg/day, n=182) or combination therapy with tenofovir (300 mg/day, n=197) for 100 weeks were randomized in terms of efficacy and safety. The combination therapy provided a greater efficacy for undetectable HBV DNA in patients with HBeAg-positive and HBV DNA≥10^8 IU/mL. There was no statistical difference between the two groups in terms of HBeAg negativity or seroconversion, if the subjects had HBV DNA≤10^8 IU/mL. Both drugs were well tolerated (31).

Tenofovir (300 mg/day) and entecavir (0.5 mg/day for naive, 1 mg/day for treatment experienced) combination, when used as a rescue therapy for 21 months in 57 patients who were partial responders or multidrug resistant, had undetectable HBV DNA in 51 out of 57 patients. The probability of HBV DNA suppression was not influenced by adefovir or entecavir resistance or advanced fibrosis by combination therapy (32).

In this study, HBV DNA negativity increased monthly from the 6th to the 24th month reaching 88.9% and then curving and plateauing up to the last visit. If patients have suboptimal virological response to tenofovir therapy by the 24th month, entecavir may be added to the tenofovir treatment. ALT normalization after tenofovir treatment increased to 70.2% by the 6th month, curving and plateauing until the last visit. Patients with high ALT levels at 6 months should be checked for other causes of increasing ALT levels, such as nonalcoholic steatohepatitis (NASH) or drug toxicity, and should be treated accordingly.

An interesting study from Hong Kong related with HBsAg, showed a decline in chronic HBV patients after 3 years of treatment with tenofovir, revealing that a significantly greater median rate of HBsAg seroquantification levels decreased during the first year, in comparison to the second and the third years. Patients with HBsAg sero-quantification levels greater than 3 log IU/mL were lesser than 3 log IU/mL and had a greater median rate of HBsAg reduction during the treatment (33).

Tenofovir nephrotoxicity is characterized by glomerular filtration abnormalities and proximal tubular cell dysfunction which may be associated with acute and chronic renal diseases. Adverse events of tenofovir treatment was reported in clinical studies as nausea; headache; nasopharyngitis; fatigue; abdominal and back pain; increase of ALT, AST, serum amylase, serum creatinine, and serum creatine kinase (34,35).

Tenofovir is one of the most potent and safest drugs for sustaining virological response in the treatment of chronic hepatitis B infection. It is effective in patients who are both naive and multidrug resistant and both HBeAg-positive and HBeAg-negative chronic hepatitis B. Treatment with tenofovir results in the regression of liver cirrhosis and fibrosis with an extension of survival. However, the effectiveness of tenofovir in the seroconversion of HBeAg and HBsAg are not satisfactory. As a result, the drugs that we had hoped would be the cure for HBV must not only have higher HBV DNA suppression and ALT normalization effects but also higher HBeAg and HBsAg seroconversion rates. More potent alternative drug treatments must be researched.

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